Clinical trial results:
A Randomized, Double-Blind, Placebo- and Active-Controlled Study of DS-5565 in Subjects with Pain Associated with Fibromyalgia

Summary

EudraCT number	2013-005162-20
Trial protocol	AT BE ES PT SI PL
Global end of trial date	12 January 2017

Results information

Result version number	v1 (current)
This version publication date	08 December 2017
First version publication date	08 December 2017

Trial information

Trial identification

Sponsor protocol code	DS5565-A-E310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02187471
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Clinical Trial Information Contact, Daiichi Sankyo, Inc., +1 7325905000, eu_cta@dsi.com
Scientific contact	Clinical Trial Information Contact, Daiichi Sankyo, Inc., +1 7325905000, eu_cta@dsi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare change in weekly average daily pain score (ADPS) from baseline to Week 13 in subjects receiving either dose of DS-5565 versus placebo.
Weekly ADPS is based on daily pain scores reported by the subject that best describes his or her worst pain over the previous 24 hours.

Protection of trial subjects:

This trial was conducted under ICH E6 Good Clinical Practice, which has its foundation in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 86
Country: Number of subjects enrolled	Portugal: 22
Country: Number of subjects enrolled	Slovenia: 11
Country: Number of subjects enrolled	Spain: 101
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Argentina: 88
Country: Number of subjects enrolled	Belarus: 12
Country: Number of subjects enrolled	Chile: 45
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Mexico: 29
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Ukraine: 74
Country: Number of subjects enrolled	United States: 760
Worldwide total number of subjects	1301
EEA total number of subjects	264

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1174
From 65 to 84 years	127
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 2526 patients screened, 1301 from 15 countries were randomized into study groups.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients take one each of placebo tablet and capsule, twice daily (BID)

Arm type	Placebo
Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet matching DS-5565 tablet

Investigational medicinal product name	Placebo capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule matching pregabalin capsule

Arm title	Pregabalin

Arm description:

Patients take one pregabalin capsule and one placebo tablet BID

Arm type	Other product - not comparator
Investigational medicinal product name	Pregabalin capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg capsule for one week, then 150 mg capsule

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Placebo tablet matching DS-5565 tablet

Arm title	DS5565 15 mg QD

Arm description:

Patients take one each of placebo tablet and capsule in the morning and one placebo capsule in the evening with one DS-5565 tablet, once daily (QD)

Arm type	Experimental
Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet matching DS-5565 tablet

Investigational medicinal product name	Placebo capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule matching pregabalin capsule

Investigational medicinal product name	DS-5565 tablet
Investigational medicinal product code	
Other name	mirogabalin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DS-5565 (mirogabalin) 15 mg tablet

Arm title	DS5565 15 mg BID

Arm description:

Patients take one DS-5565 tablet and one placebo capsule BID

Arm type	Experimental
Investigational medicinal product name	DS-5565 tablet
Investigational medicinal product code	
Other name	mirogabalin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DS-5565 (mirogabalin) 15 mg tablet

Investigational medicinal product name	Placebo capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule matching pregabalin capsule

Number of subjects in period 1	Placebo	Pregabalin	DS5565 15 mg QD
Started	325	324	326
Completed Double-Blind Treatment Period	249	242	240
Completed Tapering Period	278	269	263
Completed Follow-up	194 [1]	193 [2]	199 [3]
Entered Open-label Extension Study	99 [4]	88 [5]	84 [6]
Safety Analysis Set	324	319	324
mITT Analysis Set	324	319	324
Completed	249	242	240
Not completed	76	82	86
Consent withdrawn by subject	23	29	22
Adverse event, non-fatal	24	34	44
Missing	-	-	-
Lack of efficacy	18	9	13
Protocol deviation	4	5	4
No reason provided	7	5	3

Number of subjects in period 1	DS5565 15 mg BID
Started	326
Completed Double-Blind Treatment Period	246
Completed Tapering Period	273
Completed Follow-up	194 [7]
Entered Open-label Extension Study	100 [8]
Safety Analysis Set	323
mITT Analysis Set	323
Completed	246
Not completed	80
Consent withdrawn by subject	24
Adverse event, non-fatal	36
Missing	1
Lack of efficacy	11
Protocol deviation	4
No reason provided	4

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having

completed the trial.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients take one each of placebo tablet and capsule, twice daily (BID)	
Reporting group title	Pregabalin
Reporting group description:	
Patients take one pregabalin capsule and one placebo tablet BID	
Reporting group title	DS5565 15 mg QD
Reporting group description:	
Patients take one each of placebo tablet and capsule in the morning and one placebo capsule in the evening with one DS-5565 tablet, once daily (QD)	
Reporting group title	DS5565 15 mg BID
Reporting group description:	
Patients take one DS-5565 tablet and one placebo capsule BID	

Reporting group values	Placebo	Pregabalin	DS5565 15 mg QD
Number of subjects	325	324	326
Age categorical Units: Subjects			
Adults (18-64 years)	296	294	294
From 65-84 years	29	30	32
Gender categorical Units: Subjects			
Female	303	302	302
Male	22	22	24

Reporting group values	DS5565 15 mg BID	Total	
Number of subjects	326	1301	
Age categorical Units: Subjects			
Adults (18-64 years)	290	1174	
From 65-84 years	36	127	
Gender categorical Units: Subjects			
Female	296	1203	
Male	30	98	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Patients take one each of placebo tablet and capsule, twice daily (BID)	
Reporting group title	Pregabalin
Reporting group description:	
Patients take one pregabalin capsule and one placebo tablet BID	
Reporting group title	DS5565 15 mg QD
Reporting group description:	
Patients take one each of placebo tablet and capsule in the morning and one placebo capsule in the evening with one DS-5565 tablet, once daily (QD)	
Reporting group title	DS5565 15 mg BID
Reporting group description:	
Patients take one DS-5565 tablet and one placebo capsule BID	

Primary: Average daily pain score (ADPS) for either dose of DS-5565 versus placebo

End point title	Average daily pain score (ADPS) for either dose of DS-5565 versus placebo[1][2]
End point description:	
Average daily pain scores reported by the patient that best describes his or her worst pain over the previous 24 hours. A daily pain score has a scale of 0 = no pain to 10 = worst possible pain. For patients with no Week 13 data, the baseline observation was carried forward (BOCF).	
End point type	Primary
End point timeframe:	
Baseline, Week 13	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No further statistical analysis was performed to arrive at this summary aggregate data.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only pregabalin was included in this endpoint.

End point values	Placebo	DS5565 15 mg QD	DS5565 15 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	323	324	323	
Units: scores on a scale				
arithmetic mean (standard deviation)				
at Baseline	7.20 (± 1.393)	7.23 (± 1.357)	7.24 (± 1.436)	
at Week 13	5.53 (± 2.462)	5.51 (± 1.486)	5.30 (± 2.724)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients who answered "much improved or better" in PGIC at Week 13 receiving either dose of DS-5565 versus placebo

End point title	Number of patients who answered "much improved or better" in PGIC at Week 13 receiving either dose of DS-5565 versus placebo[3]

End point description:

Patients rated global impression of change (PGIC) on a categorical scale from 1 = very much improved to 7 = very much worse

End point type	Secondary

End point timeframe:

Baseline, Week 13

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pregabalin was not included in this endpoint.

End point values	Placebo	DS5565 15 mg QD	DS5565 15 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	324	323	
Units: Patients	85	120	129	

Statistical analyses

No statistical analyses for this end point

Secondary: Average score on the fibromyalgia index questionnaire (FIQ) in patients receiving either dose of DS-5565 or placebo

End point title	Average score on the fibromyalgia index questionnaire (FIQ) in patients receiving either dose of DS-5565 or placebo[4]

End point description:

The FIQ is composed of 10 items. The first item contains 11 questions related to physical functioning - each question is rated on a 4-point Likert-type scale. Items 2 and 3 ask the patient to mark the number of days that they feel well and the number of days they were unable to work (including housework) because of fibromyalgia (FM) symptoms. Items 4 through 10 are horizontal linear scales marked in 10 increments on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. A higher score indicates a greater impact of the syndrome on the patient. Scores were collected from patients who completed the assessment at the given time point.

End point type	Secondary

End point timeframe:

Baseline, Week 13

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pregabalin was not included in this endpoint.

End point values	Placebo	DS5565 15 mg QD	DS5565 15 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	324	323	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
at Baseline (n=322,323,320)	66.02 (± 14.071)	63.26 (± 13.822)	64.48 (± 13.615)	

at Week 13 (n=249,240,246)	47.80 (± 20.248)	43.86 (± 20.714)	41.04 (± 22.115)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients receiving either dose of DS-5565 or placebo classified as responders at Week 13

End point title	Number of patients receiving either dose of DS-5565 or placebo classified as responders at Week 13[5]

End point description:

Patients classified as responders are those with a substantial reduction in ADPS in Week 13 (BOCF) compared to baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 13

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pregabalin was not included in this endpoint.

End point values	Placebo	DS5565 15 mg QD	DS5565 15 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	324	323	
Units: Patients				
30% Responders	122	121	125	
50% Responders	68	77	89	

Statistical analyses

No statistical analyses for this end point

Secondary: Average daily pain score (ADPS) for pregabalin

End point title	Average daily pain score (ADPS) for pregabalin[6]

End point description:

Average daily pain scores reported by the patient that best describes his or her worst pain over the previous 24 hours. A daily pain score has a scale of 0 = no pain to 10 = worst possible pain. For patients with no Week 13 data, the baseline observation was carried forward (BOCF).

End point type	Secondary

End point timeframe:

Baseline, Week 13

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pregabalin was not included in this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	319			
Units: Scores on a scale				
arithmetic mean (standard deviation)				
at Baseline	7.22 (± 1.326)			
at Week 13	5.12 (± 2.510)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events that emerge or get worse on or after the first dosing of double blind study medication and during study treatment up to 4 weeks after the last dose of double blind study medication

Adverse event reporting additional description:

Total number of treatment-emergent adverse events (TEAEs) counts all occurrences in all subjects. In the system organ class and preferred term summarization, a patient was counted only once when one or more events were reported, so the occurrences mirror the number of patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients take one pregabalin capsule and one placebo tablet BID

Reporting group title	Pregabalin

Reporting group description:

Patients take one pregabalin capsule and one placebo tablet BID

Reporting group title	DS5565 15 mg QD

Reporting group description:

Patients take one each of placebo tablet and capsule in the morning and one placebo capsule in the evening with one DS-5565 tablet, once daily (QD)

Reporting group title	DS5565 15 mg BID

Reporting group description:

Patients take one DS-5565 tablet and one placebo capsule BID

Serious adverse events	Placebo	Pregabalin	DS5565 15 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 324 (2.78%)	2 / 319 (0.63%)	5 / 324 (1.54%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			

subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Uraemic encephalopathy			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure like phenomena			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	1 / 324 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	1 / 324 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	1 / 324 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	1 / 324 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis acute			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 324 (0.00%)	0 / 319 (0.00%)	1 / 324 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	0 / 324 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DS5565 15 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 323 (1.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 323 (0.31%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Animal bite			

subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Uraemic encephalopathy			
subjects affected / exposed	1 / 323 (0.31%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure like phenomena			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 323 (0.31%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis acute			
subjects affected / exposed	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection staphylococcal			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal wall abscess			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Pregabalin	DS5565 15 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	214 / 324 (66.05%)	243 / 319 (76.18%)	247 / 324 (76.23%)
Investigations			
Weight increased			
subjects affected / exposed	22 / 324 (6.79%)	49 / 319 (15.36%)	26 / 324 (8.02%)
occurrences (all)	22	49	26
Nervous system disorders			
Dizziness			
subjects affected / exposed	17 / 324 (5.25%)	56 / 319 (17.55%)	47 / 324 (14.51%)
occurrences (all)	17	56	47
Headache			

subjects affected / exposed	50 / 324 (15.43%)	41 / 319 (12.85%)	39 / 324 (12.04%)
occurrences (all)	50	41	39
Somnolence			
subjects affected / exposed	9 / 324 (2.78%)	40 / 319 (12.54%)	29 / 324 (8.95%)
occurrences (all)	9	40	29
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	10 / 324 (3.09%)	12 / 319 (3.76%)	15 / 324 (4.63%)
occurrences (all)	10	12	15
Oedema peripheral			
subjects affected / exposed	4 / 324 (1.23%)	18 / 319 (5.64%)	11 / 324 (3.40%)
occurrences (all)	4	18	11
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 324 (3.40%)	18 / 319 (5.64%)	25 / 324 (7.72%)
occurrences (all)	11	18	25
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 324 (3.40%)	11 / 319 (3.45%)	18 / 324 (5.56%)
occurrences (all)	11	11	18
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	14 / 324 (4.32%)	10 / 319 (3.13%)	20 / 324 (6.17%)
occurrences (all)	14	10	20
Nasopharyngitis			
subjects affected / exposed	13 / 324 (4.01%)	19 / 319 (5.96%)	13 / 324 (4.01%)
occurrences (all)	13	19	13

Non-serious adverse events	DS5565 15 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	247 / 323 (76.47%)		
Investigations			
Weight increased			
subjects affected / exposed	34 / 323 (10.53%)		
occurrences (all)	34		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	36 / 323 (11.15%) 36 31 / 323 (9.60%) 31 39 / 323 (12.07%) 39		
General disorders and administration site conditions Drug withdrawal syndrome subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	 21 / 323 (6.50%) 21 15 / 323 (4.64%) 15		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 20 / 323 (6.19%) 20		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 7 / 323 (2.17%) 7		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 16 / 323 (4.95%) 16 14 / 323 (4.33%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2014	Made multiple changes based on sponsor decision and FDA feedback. Amendment occurred before first subject first visit, so all changes were incorporated into the initial informed consent.
29 January 2015	Clarified and added eligibility criteria and screening methods. and increased screening window.
07 April 2016	Modified inclusion exclusion criteria to reflect DSMB's recommendation to screen for suicidality.
15 December 2016	Changed order of objectives and statistical analysis plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported